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CORRELATION OF VASCULAR ENDOTHELIAL FUNCTION AND INFLAMMATORY FACTORS WITH RENAL FUNCTION IN PATIENTS WITH DIABETIC NEPHROPATHY

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The purpose of the study was to examine the interrelation between vascular endothelial function and inflammatory factors with renal function in patients diagnosed with diabetic nephropathy. A total of 120 patients with diabetic nephropathy were enrolled in this study. The patients were categorized based on the stage of diabetic nephropathy: Group I – normoalbuminuria (n=30), Group II – microalbuminuria (n=30), Group III – macroalbuminuria (n=30), Group IV – patients with clinical nephropathy (n=30). The levels of creatinine, endothelin-1, nitric oxide, interleukin-6, interleukin-10, tumor necrosis factor-alpha in the blood and glomerular filtration rate were determined. There was a correlation between glomerular filtration rate and blood endothelin-1 (r=0.517 (p<0.01) in Group I, r=-0.74 (p<0.01) in Group III, r=-0.566 (p<0.01) in Group IV); and with tumor necrosis factor-alpha: in Group 1 (r=0.589 (p<0.01), in Group II (r=0.5451 (p<0.05), in Group III (r=-0.531 (p<0.01) and in Group IV (r=-0.64 (p<0.01). Our findings suggest significant associations between endothelial biomarkers, inflammatory factors, and renal function at various stages of diabetic nephropathy.

Key words: diabetic nephropathy, glomerular filtration rate, interleukin, endothelin-1, tumor necrosis factor-alpha

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КОРЕЛЯЦІЯ ФУНКЦІЇ СУДИННОГО ЕНДОТЕЛІЮ І ФАКТОРІВ ЗАПАЛЕННЯ З ФУНКЦІЄЮ НИРОК У ХВОРИХ З ДІАБЕТИЧНОЇ НЕФРОПАТІЄЮ

Метою дослідження було вивчити взаємозв'язок між функцією ендотелію судин та факторами запалення з нирковою функцією у пацієнтів з діагнозом діабетична нефропатія. Загалом у дослідженні взяли участь 120 пацієнтів з діабетичною нефропатією. Залежно від стадії діабетичної нефропатії пацієнти були розділені на 4 групи: I група – нормоальбумінурія (n=30), II група – мікроальбумінурія (n=30), III група – макроальбумінурія (n=30) та IV група – пацієнти з клінікою нефропатії (n = 30). Визначали рівень креатиніну, ендотеліну-1, оксиду азоту, інтерлейкіну-6, інтерлейкіну-10, фактору некрозу пухлини-альфа в крові та швидкість клубочкової фільтрації. Встановлено кореляційний зв’язок між швидкістю клубочкової фільтрації та ендотеліном-1 (r=0,517 (p<0,01) у I групі, r=-0,74 (p<0,01) у III групі r=-0,566 (p<0 ,01) у IV групі) та фактором некрозу пухлини-альфа: у I групі (r=0,589 (p<0,01), у II групі (r=0,5451 (p<0,05), у III групі (r=-0,531 (p<0,01), у IV групі (r=-0,64 (p<0,01). Наші результати свідчать про достовірний зв'язок між ендотеліальними біомаркерами, факторами запалення та функцією нирок на різних стадіях діабетичної нефропатії.

Ключові слова: діабетична нефропатія, швидкість клубочкової фільтрації, інтерлейкін, ендотелін-1, фактор некрозу пухлини-альфа.

Diabetes mellitus (DM) is at the forefront of the etiological causes of CKD [11]. Currently, the spread of DM in the world has taken on the character of a non-communicable epidemic. According to the World Health Organization (WHO), the number of patients with type 2 DM by 2025 may reach 380 million [12]. The pathogenesis of type 2 diabetes mellitus is multifaceted and is a major concern among diabetic patients. Inflammatory responses play a pivotal role in the development and progression of diabetic nephropathy. Tumor necrosis factor-alpha (TNF–alpha), interleukin-10 (IL–10) and interleukin-6 (IL–6) have a crucial role in inducing inflammatory responses within the systemic inflammatory processes, thereby modulating the patient's immune and inflammatory systems [2, 5, 10].

In the presence of proteinuria in patients with diabetic nephropathy (DN), the number of glomerular and tubulointerstitial capillaries in patients with diabetic nephropathy is lower than in a normal organism. The reduction in the number of capillaries is mainly associated with apoptosis and clearance of endothelial vascular cells [1, 8]. Early detection of endothelial dysfunction (ED) is crucial to halt the progression of DN [6, 9]. In addition, patients with stage I-II chronic kidney disease have a low level of adherence, which may be an additional risk factor for renal failure progression [7]. An approach to assess endothelial function involves studying factors that induce damage to the endothelium, and their plasma levels are correlated with ED. Thus, examining the associations between vascular endothelial function, inflammatory factors, and renal function in individuals with diabetic nephropathy could yield valuable clinical insights, offering a novel reference point for the diagnosis and management of patients afflicted by this condition.

The purpose of the study was to examine the interrelation between vascular endothelial function and inflammatory factors with renal function in patients diagnosed with diabetic nephropathy.

Materials and methods. A total of 120 patients with diabetic nephropathy (DN), aged between 25 and 65 years (mean age 49.9±0.81 years), who were receiving inpatient treatment, were enrolled in this study. Among them, there were 60 female patients (50 %) and 60 male patients (50 %). The examination and treatment of the patients were carried out at the Department of Internal Medicine I, Azerbaijan Medical University (AMU), and the Nephrology and Endocrinology Departments of the Educational-Therapeutic Clinic at AMU. Exclusion criteria comprised patients older than 65 years, those with type 1 diabetes, oncological diseases, chronic lung diseases, history of myocardial infarction, neurological disorders, and uncontrolled arterial hypertension. The patients were categorized into four groups based on the stage of DN: Group I – normoalbuminuria (n=30), Group II – microalbuminuria (n=30), Group III – macroalbuminuria (n=30), and Group IV – patients with clinical nephropathy (n=30). All patients included in the study underwent comprehensive clinical and laboratory investigations. General and biochemical blood analyses were conducted, measuring levels of creatinine, urea, uric acid, cystatin C, and lipid profile. Additionally, endothelial function markers such as endothelin-1 (En–1), nitric oxide (NO), and interleukin-6 (IL–6), interleukin-10 (IL–10), and tumor necrosis factor-alpha (TNF–alpha) were determined in the blood. Glomerular filtration rate (GFR) was estimated using the CKD-EPI formula based on the determination of creatinine levels. Based on the goal and objectives, the results were processed by statistical methods. To characterize groups of homogeneous units, the arithmetic mean (M), standard error (m) and range of change were determined. To study the qualitative indicators, the absolute number of groups and their percentage were determined. To compare quantitative indicators, the nonparametric Mann-Whitney test was used, which evaluates the difference between the indicators. At the same time, the statistical difference $p<0.05$ was assessed as significant.For a statistical study of the cause-and-effect relationship, a non-parametric method was used - the Spearman rank correlation coefficient. This method determines the measure of linear relationship between random variables. When using rank correlation, if the correlation coefficient between the indicators is 0.3 or less, then the correlation is considered weak, if 0.4–0.7 is medium, 0.7 and above is high.

Results of the study and their discussion. In the course of the conducted research on diabetic nephropathy, the relationship between renal functional state and endothelial function was investigated. As diabetic nephropathy progressed and the GFR declined, the concentration of endothelin-1 (En–1) in the blood significantly increased. The elevation of blood En–1 concentration in diabetic nephropathy indicates impaired endothelial vasomotor function. Correlation analysis revealed a direct correlation between GFR and blood En–1 concentration in the early stages and an inverse correlation in the last two stages of diabetic nephropathy. This correlation amounted to r=0.517 ($p<0.01$) in the first group, r=0.27 ($p>0.05$) in the second group, r=-0.74 ($p<0.01$), r=-0.566 ($p<0.01$) in the fourth group, respectively (Fig. 1).

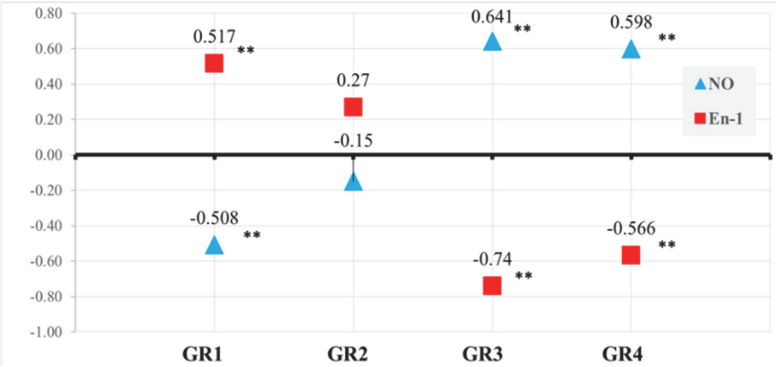

Fig. 1. The correlation between GFR and the levels of endothelin-1 (En-1) and NO at different stages of diabetic nephropathy.

Note: * – correlation is significant at the 0.05 level; ** – correlation is significant at the 0.01 level.

The study also revealed an inverse correlation between the concentration of another endothelial biomarker – nitric oxide (NO) in the blood, and GFR in the early stages of DN, while a positive correlation was observed at the 3rd and 4th stages. As GFR decreased, endothelial damage and its proliferative activity increased. In these groups, an inverse correlation was found between tumor necrosis factor-alpha (TNF–alpha), which is considered an inflammatory marker of endothelial function, and GFR (Fig. 2).

Specifically, this relationship was observed as follows: in Group 1, the correlation coefficient was r=0.589 ($p<0.01$), in Group 2, it was r=0.5451 ($p<0.05$), in Group 3, it was r=-0.531 ($p<0.01$), and in Group 4, it was r=-0.64 ($p<0.01$).

The correlation between flow-mediated dilation (FMD) and inflammatory markers was also investigated in the groups. In all groups, an inverse correlation was observed between tumor necrosis factor-alpha (TNF–alpha) and FMD. The correlation coefficients were as follows: r=-0.751, $p<0.01$ in Group I; r=-0.684, $p<0.01$ in Group II; r=-0.635, $p<0.01$ in Group III; and r=-0.668, $p<0.01$ in Group IV. Changes in interleukin-6 (IL–6) and interleukin-10 (IL–10), which are inflammation markers, showed

different patterns. Although an inverse relationship between IL–10 and FMD was observed, it was not statistically significant. Additionally, an inverse correlation between IL–6 and FMD was detected. While it did not reach statistical significance in the 1st and 2nd stages of diabetic nephropathy, a statistically significant correlation was found in the 3rd and 4th groups (r=-0.592 in Group III, p<0.01, and r=-0.547 in Group IV, p<0.01).

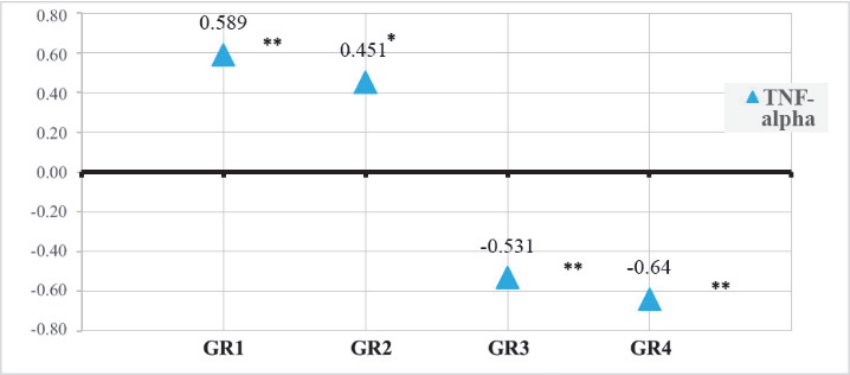

Fig. 2. The correlation between GFR and the marker of tumor necrosis factor–alpha (TNF–alpha) at different stages of diabetic nephropathy.

Note: * – correlation is significant at the 0.05 level; ** – correlation is significant at the 0.01 level.

The dysregulation of blood glucose in the body leads to dysfunction in various target organs. Among the complications frequently encountered in clinical settings, vascular disease stands out as a common ailment. Diabetic nephropathy represents one of the most prevalent complications, characterized by impaired renal function and the presence of proteinuria [8]. The global percentage of the prevalent end-stage renal disease patients with diabetes increased worldwide [4]. This condition is a leading cause of chronic renal failure, and its pathogenesis is heavily influenced by the hyperactive inflammatory system [6, 15].

In various sources we found out, that despite all novel findings, there are not significant data about real markers for early diagnosis of DN. So, Mizdrak M, et al, in their review aimed to provide comprehensive insight into diagnostic methods available for early detection of chronic kidney disease (CKD). The authors discussed the following markers: omics, microbiota indicators, microRNA etc. and found that none of these biomarkers have met the criteria of an ideal early marker [11].

In our study the correlation between endothelial biomarkers, inflammatory factors, and renal function were revealed. Chavarria-Buenrostro LE, et al, conducted a case-control study on 128 patients with DN and 150 control subjects from western Mexico. All patients were tested for IL–10 polymorphisms. According to their results, there were no correlations between IL–10 haplotypes and clinical parameters in patients with DN. But the authors noted that some IL–10 haplotypes have a higher risk factor to develop DN [3].

Additionally, Sanchez-Alamo B, et al, emphasized that IL–6 is independently associated with an increased risk for progression of diabetic kidney disease. They conducted Multivariate Cox regression analysis, which showed that baseline IL–6 levels >4.84 pg/mL (HR 4.10, 95 % CI 1.36–12.31) were a risk factor for reaching the primary endpoint adjusted for GFR and proteinuria. [13]. These results are partially similar with ours: correlation between IL–6 and FMD, which did not reach statistical significance in the 1st and 2nd stages of diabetic nephropathy, but had a statistically significant correlation in the groups with severe renal dysfunction.

We found out an inverse correlation between tumor necrosis factor-alpha and glomerular filtration rate. El-Edel RH, et al, studied the role of tumor necrosis factor alpha in type 2 diabetic nephropathy and revealed that serum level of TNF–α in DM-CKD was significantly higher than controls and DM (P<0.001). Moreover, there was a significant positive correlation between serum levels of TNF–α and fasting blood glucose, creatinine, total cholesterol, low-density lipoprotein-cholesterol, glycated hemoglobin, and microalbumin/creatinine ratio among DM-CKD group (r=0.042, <0.001, <0.001, <0.001, 0.027, and 0.043, respectively). Thus, serum TNF-α was significantly increased in patients with DM and DM-CKD but was higher in patients with DM-CKD, which designates that TNF–α can participate in progression of DM to DN and might play an important role in mediating DN [5].

Type 2 diabetes mellitus often accompanies metabolic imbalances in adipocytes, resulting in elevated levels of inflammatory factors and consequent inflammatory responses [13, 14]. Agayev M, et al, studying the relationship between the level of blood lipids and the endothelial function in patients with different stages of chronic kidney disease revealed, that endothelial disorders were more pronounced in patients with high cholesterol, LDL-C and serum triglycerides and they were lower in patients with high HDL-C. Increasing severity of chronic kidney disease was accompanied by more pronounced impairment

of the endothelial dysfunction which may be due to the lipid metabolism disorder. But in our study we did not determine the association between lipid metabolism and renal function, it will be the goal of our further works.

Sato Y, et al, studying the role of immune cells and inflammation in acute kidney injury to chronic kidney disease progression, noted that age-dependent structural and functional impairment of kidneys, more precise understanding of chronic inflammation driven by inflammaging and immunosenescence will eventually resolve many of the issues in this field and facilitate the development of therapies [14]. The combination of diabetes and renal injury further exacerbates the ongoing inflammatory system response [3].

Conclusion

These findings suggest significant associations between endothelial biomarkers, inflammatory factors, and renal function at various stages of diabetic nephropathy, shedding light on potential mechanisms underlying the disease progression. Further investigations are warranted to explore these relationships in greater depth and may open new avenues for the development of targeted therapeutic interventions.

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